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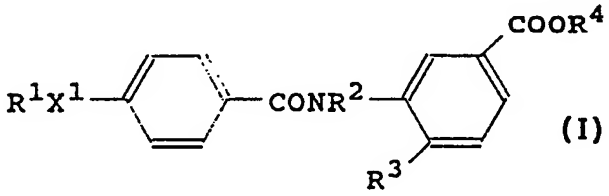

(I)

(57) Abstract

Benzanilide derivatives of formula (I) wherein R^1 represents alkyl, optionally interrupted by one or more hetero atoms, X^1 represents oxygen, sulphur or $-NR^5-$ wherein R^5 represents hydrogen or alkyl or alkanoyl optionally substituted by halogen, R^2 represents hydrogen or alkyl, R^3 represents alkyl, alkoxy, alkylthio, dimethylamino or a heterocyclo group containing at least one nitrogen atom and linked via that nitrogen atom to the rest of the molecule, or a halogen atom, and R^4 represents alkyl containing up to 10 carton atoms, optionally containing one or more carbon-carbon double or triple bonds, and optionally interrupted by one or more hetero atoms.

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BENZANILIDE DERIVATIVES AND THEIR USE AS ANTI-ANTHEROSCLEROTIC AGENTS

This invention relates to new, therapeutically useful benzanilide derivatives, to a process for their production and to pharmaceutical compositions containing them, and methods for their use.

The new benzanilide derivatives of the present invention are the compounds of formula I, hereinafter depicted, wherein R^1 represents a straight- or branched-chain alkyl group containing from about 4 to about 20 carbon atoms, optionally interrupted by one or more hetero atoms, e.g. oxygen, sulphur or nitrogen atoms, preferably an alkyl, alkoxyalkyl, alkylaminoalkyl or dialkylaminoalkyl group containing from about 4 to about 20 carbon atoms, X^1 represents an oxygen or sulphur atom or a group $-NR^5-$ wherein R^5 represents a hydrogen atom or a straight- or branched-chain alkyl or alkanoyl group containing up to about 5 carbon atoms, optionally substituted by one or more halogen, e.g. chlorine or fluorine, atoms, R^2 represents a hydrogen atom or a straight- or branched-chain alkyl group containing from 1 to about 4 carbon atoms, R^3 represents a straight- or branched-chain alkyl, alkoxy or alkylthio group containing from 1 to about 4 carbon atoms or a dimethylamino group or a 5- to 8-membered heterocyclo group containing at least one nitrogen atom and linked via that nitrogen atom to the rest of the molecule, e.g. an

imidazol-1-yl or pyrrolidin-1-yl group, or a halogen, e.g. chlorine or fluorine, atom, and R^4 represents a straight- or branched-chain alkyl group containing up to about 10 carbon atoms, optionally containing one or more carbon-carbon double or triple bonds, and optionally interrupted by one or more hetero atoms, e.g. oxygen, sulphur or nitrogen atoms, preferably an alkyl, alkoxyalkyl, alkylaminoalkyl or dialkylaminoalkyl group containing up to about 10 carbon atoms.

As will be apparent to those skilled in the art, some of the compounds of formula I exhibit optical isomerism. All such forms, and their mixtures, are embraced by the invention.

Especially important compounds of the present invention include those wherein at least one of the symbols has a value selected from the following:-

(i) R^1 represents an alkyl group containing from 8 to 12, e.g. 10, carbon atoms;

(ii) X^1 represents an oxygen atom;

(iii) R^2 represents a hydrogen atom;

(iv) R^3 represents an alkoxy or alkylthio group containing 1 or 2 carbon atoms, a dimethylamino group or a halogen, e.g. chlorine or fluorine, atom; and/or

(v) R^4 represents a straight- or branched-

chain alkyl group containing up to 5 carbon atoms, optionally containing a carbon-carbon double bond or interrupted by an oxygen atom;

the other symbols being as hereinbefore defined.

Important compounds according to the invention include:-

A methyl 3-(4-decyloxybenzamido)-4-methoxybenzoate;

B 3-methylbutyl 3-(4-decyloxybenzamido)-4-methoxybenzoate;

C 3-methylbut-2-enyl 3-(4-decyloxybenzamido)-4-methoxybenzoate;

D methyl 4-chloro-3-(4-decyloxybenzamido)benzoate;

E methyl 3-(4-decyloxybenzamido)-4-fluorobenzoate;

F methyl 3-(4-decyloxybenzamido)-4-(methylthio)-benzoate;

G 3-methylbut-2-enyl 3-(4-decyloxybenzamido)-4-(methylthio)benzoate;

H butyl 3-(4-decyloxybenzamido)-4-(methylthio)-benzoate;

I ethyl 3-(4-decyloxybenzamido)-4-(ethylthio)-benzoate;

J ethyl 3-(4-decyloxybenzamido)-4-ethoxybenzoate;

K 3-methylbut-3-enyl 3-(4-decyloxybenzamido)-4-(methylthio)benzoate;

L 2-methoxyethyl 3-(4-decyloxybenzamido)-4-(methylthio)benzoate; and

M methyl 3-(4-decyloxybenzamido)-4-dimethylaminobenzoate.

The letters A to M are allocated to compounds for easy reference later in this specification.

The compounds according to the invention are inhibitors of acyl coenzyme-A:cholesterol-O-acyl transferase (ACAT;EC 2.3.1.26). They are therefore of value as anti-atherosclerotic agents and have utility in the treatment of atherosclerosis, hyperlipidaemia, cholesterol ester storage disease and atheroma in vein grafts.

Compounds within the scope of the present invention exhibit positive pharmacological activities as demonstrated by the following in vitro tests which are believed to correlate to pharmacological activity in humans and other animals.

In assays performed in vitro microsomes (prepared from the livers of rats fed a diet supplemented with 0.5%w/w cholesterol and 0.25%w/w cholic acid for 7 days) were incubated with radiolabelled oleoyl-CoA in the presence of compounds according to the invention at a concentration of 1μg/ml. The degree of ACAT inhibition produced was up to 95%.

Compounds of formula I can be prepared by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature.

According to a feature of the present invention, compounds of general formula I are prepared by the reaction of a compound of general formula II hereinafter depicted, wherein R^2, R^3 and R^4 are as hereinbefore defined, with a compound of general formula III, hereinafter depicted, wherein R^1 and X^1 are as hereinbefore defined and Z^1 represents a halogen, e.g. chlorine, atom.

The reaction may be performed in the presence of a suitable base, such as a tertiary amine, and may be carried out in a suitable solvent, e.g. dichloromethane, optionally with heating.

According to a further feature of the invention, compounds of formula I are prepared by reacting a compound of general formula:

$$R^4OH \qquad (IV)$$

wherein R^4 is as hereinbefore defined, with a compound of formula V, hereinafter depicted, wherein R^1, R^2, R^3 and X^1 are as hereinbefore defined and Z^2 represents a halogen, e.g. chlorine, atom or a hydroxy group.

When Z^2 represents a halogen atom the reaction may be performed in the presence of a suitable base, such as a tertiary amine.

When Z^2 represents a hydroxy group the reaction is preferably performed in the presence of a condensing agent, such as dicyclohexylcarbodiimide, or a catalytic quantity of an inorganic acid, e.g. hydrochloric acid, optionally prepared in situ.

In each instance the reaction may be carried out in a suitable solvent, e.g. dichloromethane, optionally with heating.

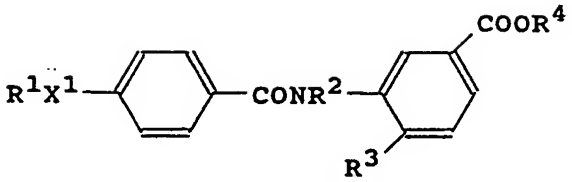
According to a further feature of the invention, compounds of general formula I are prepared by the interconversion of other compounds of formula I. For example, compounds wherein R^2 represents a straight- or branched-chain alkyl group containing from 1 to 4 carbon atoms may be prepared from compounds of formula I wherein R^2 represents a hydrogen atom by alkylation by the application or adaptation of known methods.

Compounds of formulae II, III, IV and V may be prepared by the application or adaptation of known methods.

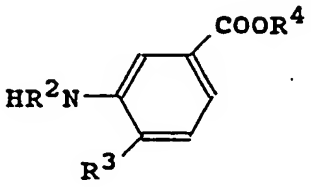
For example, (i) acid halides of formula V wherein Z^2 represents a halogen atom may be prepared from the corresponding carboxylic acids of formula V wherein Z^2 represents a hydroxy group by known methods,

e.g., when Z^2 represents a chlorine atom, by reaction with thionyl chloride;

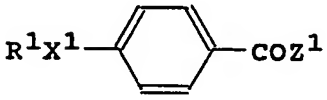
(ii) the corresponding carboxylic acids of formula V wherein Z^2 represents a hydroxy group may be prepared from compounds of formula I by hydrolysis of the ester grouping $-COOR^4$ by known methods, for example by reaction with alkali, e.g. aqueous sodium hydroxide solution, followed by neutralisation by treatment with mineral acid, e.g. dilute hydrochloric acid.


COOR4
R1X1
CONR2
R3

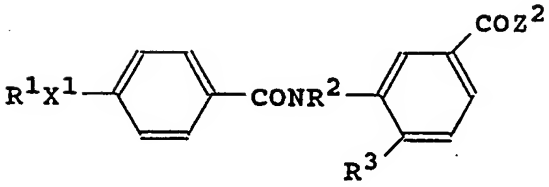
I


COOR4
HR2N
R3

II


R1X1
COZ1

III


COZ2
R1X1
CONR2
R3

V

The following Examples illustrate the preparation of the compounds according to the invention and the Reference Example illustrates the preparation of the intermediates.

EXAMPLE 1

Compounds A, D, E, F, I and J

A stirred solution of methyl 3-amino-4-methoxybenzoate (5.49g) and triethylamine (4.55g) in dichloromethane (120ml) was treated with 4-decyloxybenzoyl chloride (9.0g; prepared from 4-decyloxybenzoic acid and thionyl chloride) and the mixture was stirred for 2 hours. The reaction mixture was then poured into water, the organic layer was separated and washed with hydrochloric acid (50ml; 1N), with aqueous sodium hydroxide solution (50ml; 1N), and with water (100ml), and then it was dried over magnesium sulphate. The solution was concentrated under reduced pressure, to give an oil that solidified on standing. The solid was recrystallised from methanol, to give methyl 3-(4-decyloxybenzamido)-4-methoxybenzoate (3.2g), in the form of colourless needles, m.p. 84-85°C. [Elemental analysis:- C,70.9;H,8.2;N,3.03%; calculated:- C,70.72;H,7.99;N,3.17%].

By proceeding in a similar manner, but replacing the methyl 3-amino-4-methoxybenzoate by the appropriate quantity of methyl 3-amino-4-chlorobenzoate, and

working-up the reaction by concentrating under reduced pressure and crystallising the residue from aqueous acetone and then from toluene, there was prepared methyl 4-chloro-3-(4-decyloxybenzamido)benzoate, in the form of colourless crystals, m.p. 106-107°C. [Elemental analysis:- C,67.5;H,7.3;N,2.93;Cl,8.0%; calculated:- C,67.32;H,7.23;N,3.13;Cl,7.95%].

By proceeding in a similar manner, but replacing the methyl 3-amino-4-methoxybenzoate by the appropriate quantity of methyl 3-amino-4-fluorobenzoate, stirring at the ambient temperature for 2 hours, heating at reflux for 1 hour and working-up the reaction by concentrating under reduced pressure and crystallising the residue from aqueous acetone and then from toluene, there was prepared methyl 3-(4-decyloxybenzamido)-4-fluorobenzoate, in the form of colourless crystals, m.p. 105-106°C. [Elemental analysis:- C,69.5;H,7.6; N,3.13;F,4.47%; calculated:- C,69.90;H,7.51;N,3.26; F,4.42%].

By proceeding in a similar manner, but replacing the methyl 3-amino-4-methoxybenzoate by the appropriate quantity of methyl 3-amino-4-(methylthio)benzoate, there was prepared methyl 3-(4-decyloxybenzamido)-4-(methylthio)benzoate in the form of a cream powder, m.p. 97-99°C. [Elemental analysis:- C,67.9;H,7.63; N,2.9;S,7.1%; calculated:- C,68.27;H,7.66;N,3.07;

S,7.00%].

By proceeding in a similar manner, but replacing the methyl 3-amino-4-methoxybenzoate by the appropriate quantity of ethyl 3-amino-4-(ethylthio)benzoate and working-up the reaction by concentrating under reduced pressure and crystallising the residue from aqueous ethanol, there was prepared ethyl 3-(4-decyloxybenzamido)-4-(ethylthio)benzoate in the form of white crystals, m.p. 91-93°C. [Elemental analysis:- C,69.4;H,8.09;N,2.85;S,6.3%; calculated:- C,69.24; H,8.09;N,2.88;S,6.60%].

By proceeding in a similar manner, but replacing the methyl 3-amino-4-methoxybenzoate by the appropriate quantity of ethyl 3-amino-4-ethoxybenzoate and working-up the reaction by concentrating under reduced pressure and crystallising the residue from aqueous ethanol, there was prepared ethyl 3-(4-decyloxybenzamido)-4-ethoxybenzoate, in the form of white crystals; m.p. 89-91°C. [Elemental analysis:- C,71.3;H,8.3;N,2.9%; calculated:- C,71.61;H,8.37;N,2.98%].

EXAMPLE 2

Compound B

Ice-cold 3-methylbutan-1-ol (5ml) was treated with acetyl chloride (0.8ml) followed, after 10 minutes, by 3-(4-decyloxybenzamido)-4-methoxybenzoic acid (2.0g). The suspension was warmed on a steam

bath for 3 hours and then the mixture was partitioned between water (50ml) and dichloromethane (50ml). The organic solution was dried and concentrated under reduced pressure to give a white solid, which was chromatographed on silica gel, eluting with dichloromethane, and recrystallised from methanol, to give 3-methylbutyl 3-(4-decyloxybenzamido)-4-methoxybenzoate (0.97g), in the form of colourless needles, m.p. 66-68°C. [Elemental analysis:- C,71.9;H,8.8;N,2.6%; calculated:- C,72.43;H,8.65;N,2.82%].

EXAMPLE 3

Compounds C, G and H

A mixture of 3-(4-decyloxybenzamido)-4-methoxybenzoyl chloride [2.22g; prepared from 3-(4-decyloxybenzamido)-4-methoxybenzoic acid and thionyl chloride in dichloromethane], 3-methylbut-2-en-1-ol (2.58g) and triethylamine (3ml) in toluene (100ml) was heated at 100°C for 3 hours. The mixture was cooled and then treated with water (50ml), diethyl ether (30ml) and hydrochloric acid (5ml;2N), and the organic layer was removed and dried. Concentration under reduced pressure left an oil which solidified on standing. The solid was chromatographed on silica gel, eluting with dichloromethane, and recrystallised from methanol, to give 3-methylbut-2-enyl 3-(4-decyloxybenzamido)-4-

methoxybenzoate (1.66g), in the form of a colourless solid, m.p. 60-62°C. [Elemental analysis:- C,72.6; H,8.4;N,2.84%; calculated:- C,72.69;H,8.34;N,2.83%].

By proceeding in a similar manner, but replacing the 3-(4-decyloxybenzamido)-4-methoxybenzoic acid by the appropriate quantity of 3-(4-decyloxybenzamido)-4-(methylthio)benzoic acid and purifying the crude product by crystallisation from ethanol, instead of chromatography, there was prepared 3-methylbut-2-enyl 3-(4-decyloxybenzamido)-4-(methylthio)benzoate in the form of a white solid, m.p. 107-109°C. [Elemental analysis:- C,70.3;H,8.1;N,2.64;S,6.5%; calculated:- C,70.42;H,8.07;N,2.74;S,6.26%].

By proceeding in a similar manner, but replacing the 3-methylbut-2-en-1-ol by the appropriate quantity of butan-1-ol and purifying the crude product by crystallisation from aqueous ethanol instead of chromatography, there was prepared butyl 3-(4-decyloxybenzamido)-4-(methylthio)benzoate, in the form of a cream-coloured powder, m.p. 89-91°C. [Elemental analysis:- C,70.1;H,8.5;N,2.71;S,6.5%; calculated:- C,69.70;H,8.27;N,2.80;S,6.42%].

EXAMPLE 4

Compounds K and L

3-Methylbut-3-en-1-ol (2.0ml) was treated with a solution of 3-(4-decyloxybenzamido)-4-(methylthio)-

benzoyl chloride (2.31g) in toluene (20ml) [prepared from 3-(4-decyloxybenzamido)-4-(methylthio)benzoic acid and thionyl chloride in toluene], and the mixture was stirred vigorously. It was then treated with triethylamine (1ml) and the mixture was left to stand at the ambient temperature for 18 hours. The mixture was then diluted with dichloromethane (100ml) and washed with water (100ml), dried over magnesium sulphate and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel, eluting with a mixture of dichloromethane and methanol, and recrystallised from diethyl ether, to give 3-methylbut-3-enyl 3-(4-decyloxybenzamido)-4-(methylthio)benzoate (0.45g), in the form of a colourless solid, m.p. 91-93°C. [Elemental analysis:- C,70.4;H,8.1;N,2.63;S,6.32%; calculated:- C,70.42;H,8.07;N,2.74;S,6.26%].

By proceeding in a similar manner, but replacing the 3-methyl-but-3-en-1-ol by the appropriate quantity of 2-methoxyethanol and omitting the aqueous wash stage, there was prepared 2-methoxyethyl 3-(4-decyloxy-benzamido)-4-(methylthio)benzoate, in the form of a colourless solid, m.p. 88-90°C. [Elemental analysis:- C,67.3;H,7.8;N,2.76;S,6.56%; calculated:- C,67.03;H,7.84;N,2.79;S,6.39%].

EXAMPLE 5

Compound M

By proceeding in a manner similar to that described hereinbefore in Example 1, but replacing the methyl 3-amino-4-methoxybenzoate by the appropriate quantity of methyl 3-amino-4-dimethylaminobenzoate and omitting the acid and base washes from the work-up, there was prepared methyl 3-(4-decyloxybenzamido)-4-dimethylaminobenzoate in the form of a white solid, m.p. 77-78°C (recrystallised from a mixture of ethyl acetate and petrol [Elemental analysis:- C,71.7;H,8.5; N,6.1%; calculated:- C,71.34;H,8.42;N,6.16%].

REFERENCE EXAMPLE 1

A mixture of methyl 3-(4-decyloxybenzamido)-4-methoxybenzoate (3.31g) and aqueous sodium hydroxide solution (10ml;2N) in ethanol (100ml) was heated at reflux for 2 hours. The mixture was concentrated under reduced pressure, then diluted with water (150ml) and washed with dichloromethane (50ml). The aqueous fraction was acidified to pH1 by treatment with dilute hydrochloric acid, and extracted with dichloromethane (2x50ml). This extract was dried and concentrated under reduced pressure, and the resulting solid was recrystallised from methanol, to give 3-(4-decyloxy-benzamido)-4-methoxybenzoic acid (1.5g), in the form of a colourless solid, m.p. 194-196°C. [Elemental analysis:- C,69.7;H,7.6;N,3.0%; calculated:- C,70.23; H,7.78;N,3.28%].

The present invention also includes within its scope pharmaceutical formulations which comprise at least one of the compounds of formula I in association with a pharmaceutically acceptable carrier or coating. In clinical practice the compounds of the present invention may be administered parenterally, rectally or orally.

Solid compositions for oral administration include compressed tablets, pills, powders and granules. In such solid compositions, one or more of

the active compounds is, or are, admixed with at least one inert diluent such as starch, sucrose or lactose. The compositions may also comprise, as is normal practice, additional substances other than inert diluents, e.g. lubricating agents, such as magnesium stearate.

Liquid compositions for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art such as water and liquid paraffin. Besides inert diluents such compositions may comprise adjuvants, such as wetting and suspending agents, and sweetening, flavouring, perfuming and preserving agents. The compositions according to the invention for oral administration also include capsules of absorbable material such as gelatin, containing one or more of the active substances with or without the addition of diluents or excipients.

Preparations according to the invention for parenteral administration include sterile aqueous, aqueous-organic, and organic solutions, suspensions and emulsions. Examples of organic solvents or suspending media are propylene glycol, polyethylene glycol, vegetable oils such as olive oil and injectable organic esters such as ethyl oleate. The compositions may

also contain adjuvants such as stabilising, preserving, wetting, emulsifying and dispersing agents. They may be sterilised, for example, by filtration through a bacteria-retaining filter, by incorporation in the compositions of sterilising agents, by irradiation or by heating. They may also be manufactured in the form of sterile solid compositions, which can be dissolved in sterile water or some other sterile injectable medium immediately before use.

Solid compositions for rectal administration include suppositories formulated in accordance with known methods and containing at least one compound of formula I.

The percentage of active ingredient in the compositions of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage shall be obtained. Obviously, several unit dosage forms may be administered at about the same time. The dose employed will be determined by the physician, and depends upon the desired therapeutic effect, the route of administration and the duration of the treatment, and the condition of the patient. In the adult, the doses are generally from about 0.5 to about 70, preferably about 1 to about 10, mg/kg body weight per day by oral administration.

The following Example illustrates pharmaceutical compositions according to the present invention.

COMPOSITION EXAMPLE 1

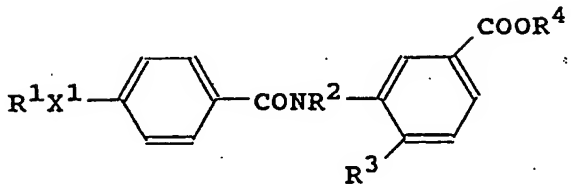
No. 2 size gelatin capsules each containing:-

3-methylbut-2-enyl 3-(4-decyloxybenzamido)-4-(methylthio)benzoate	20 mg
lactose	100 mg
starch	60 mg
dextrin	40 mg
magnesium stearate	1 mg

were prepared in accordance with the usual procedure.

CLAIMS

1. A benzanilide derivative of the formula:



I

wherein R^1 represents a straight- or branched-chain alkyl group containing from 4 to 20 carbon atoms, optionally interrupted by one or more hetero atoms, X^1 represents an oxygen or sulphur atom or a group $-NR^5-$ wherein R^5 represents a hydrogen atom or a straight- or branched-chain alkyl or alkanoyl group containing up to about 5 carbon atoms, optionally substituted by one or more halogen atoms, R^2 represents a hydrogen atom or a straight- or branched-chain alkyl group containing from 1 to 4 carbon atoms, R^3 represents a straight- or branched-chain alkyl, alkoxy or alkylthio group containing from 1 to 4 carbon atoms or a dimethylamino group or a 5- to 8-membered heterocyclo group containing at least one nitrogen atom and linked via that nitrogen atom to the rest of the molecule, or a halogen atom, and R^4 represents a straight- or branched-chain alkyl group containing up to 10 carbon atoms, optionally containing one or more carbon-carbon double or triple

bonds, and optionally interrupted by one or more hetero atoms.

2. A compound according to claim 1 wherein R^1 represents an alkyl, alkoxyalkyl, alkylaminoalkyl or dialkylaminoalkyl group containing from 4 to 20 carbon atoms, the heterocyclo group represented by R^3 is an imidazol-1-yl or pyrrolidin-1-yl group; R^4 represents an alkyl, alkoxyalkyl, alkylaminoalkyl or dialkylaminoalkyl group containing up to about 10 carbon atoms; and wherein halogen atoms are fluorine or chlorine.

3. A compound according to claim 1 wherein at least one of the symbols has a value selected from the following:

(i) R^1 represents an alkyl group containing from 8 to 12 carbon atoms;

(ii) X^1 represents an oxygen atom;

(iii) R^2 represents a hydrogen atom;

(iv) R^3 represents an alkoxy or alkylthio group containing 1 or 2 carbon atoms, a dimethylamino group or a halogen atom; and/or

(v) R^4 represents a straight- or branched-chain alkyl group containing up to 5 carbon atoms, optionally containing a carbon-carbon double bond or interrupted by an oxygen atom;

the other symbols being as hereinbefore defined.

4. A compound according to any one of the

preceding claims wherein R^1 represents an alkyl group containing 10 carbon atoms.

5. A compound according to claim 1 which is:

methyl 3-(4-decyloxybenzamido)-4-methoxybenzoate;

3-methylbutyl 3-(4-decyloxybenzamido)-4-methoxybenzoate:

3-methylbut-2-enyl 3-(4-decyloxybenzamido)-4-methoxybenzoate;

methyl 4-chloro-3-(4-decyloxybenzamido)benzoate;

methyl 3-(4-decyloxybenzamido)-4-fluorobenzoate;

methyl 3-(4-decyloxybenzamido)-4-(methylthio)-benzoate;

3-methylbut-2-enyl 3-(4-decyloxybenzamido)-4-(methylthio)benzoate;

butyl 3-(4-decyloxybenzamido)-4-(methylthio)-benzoate;

ethyl 3-(4-decyloxybenzamido)-4-(ethylthio)-benzoate;

ethyl 3-(4-decyloxybenzamido)-4-ethoxybenzoate;

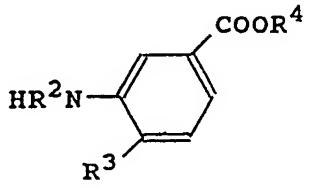
3-methylbut-3-enyl 3-(4-decyloxybenzamido)-4-(methylthio)benzoate;

2-methoxyethyl 3-(4-decyloxybenzamido)-4-(methylthio)benzoate; or

methyl 3-(4-decyloxybenzamido)-4-dimethylamino-benzoate.

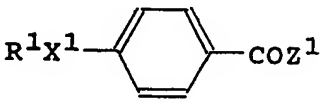
6. A process for the preparation of a benzanilide derivative according to claim 1 which comprises:

(A) the reaction of a compound of the general formula:



II

wherein R^2, R^3 and R^4 are as defined in claim 1, with a compound of the general formula :



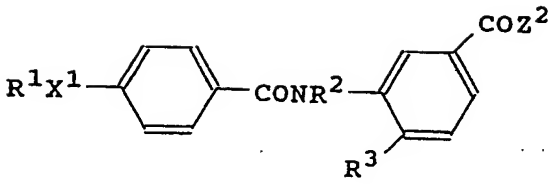
III

wherein R^1 and X^1 are as defined in claim 1 and Z^1 represents a halogen atom;

(B) the reaction of a compound of the general formula:

R^4OH IV

wherein R^4 is as defined in claim 1 with a compound of the general formula :



V

wherein R^1, R^2, R^3 and X^1 are as defined in claim 1 and Z^2 represents a halogen atom or a hydroxy group;
optionally followed by the conversion of a compound of general formula (I) into another compound of general formula (I).

7. A pharmaceutical composition which comprises a benzanilide derivative according to claim 1 in association with a pharmaceutically acceptable carrier or coating.

8. A pharmaceutical composition useful in the treatment of a condition which can be ameliorated by administration of an inhibitor of acyl coenzyme-A:cholesterol-O-acyl transferase which comprises a benzanilide derivative according to claim 1 in association with a pharmaceutically acceptable carrier or coating.

9. A method for the treatment of a condition which can be ameliorated by an inhibitor of acyl coenzyme-A:cholesterol-O-acyl transferase which comprises the administration of a benzanilide derivative according to claim 1.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 91/01376

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 C 235/56 A 61 K 31/245 C 07 C 323/63

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 C 235/00 C 07 C 323/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	EP,A,0232199 (CENTRE INTERNATIONALE DE RECHERCHES DERMATOLOGIQUES) 12 August 1987, see examples 1-14, 22, 26; claims	1-7
A	EP,A,0003532 (BYK GULDEN LOMBERG CHEMISCHE FABRIK) 22 August 1979, see examples; claims	1-7
A	WO,A,8603199 (ITALFARMACO) 5 June 1986, see examples 15,16; claims	1-7
A	US,A,4882357 (CREGER et al.) 21 November 1989, see the whole document	1-9
P,A	EP,A,0424194 (RHONE-POULENC SANTE) 24 April 1991, see the whole document	1-9

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
07-11-1991	09-12-91
International Searching Authority	Signature of Authorized Officer
EUROPEAN PATENT OFFICE	Mme. M. van der Drift

Form PCT/ISA/210 (second sheet) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9101376 SA 50459

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 03/12/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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